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# **Reliable exclusion of prognostically significant coronary disease in left ventricular dysfunction by cardiac MRI.**

## **Abbreviations**

AHA, American Heart Association

CAD, Coronary artery disease

CMR, Cardiac magnetic resonance

ESC, European Society of Cardiology

HFREF, Heart failure with reduced ejection fraction

HRA, Health Research Authority

LAD, Left anterior descending

LCx, Left circumflex artery

LGE, Late gadolinium enhancement

LV, Left ventricle

LVEDVI, Left ventricular end diastolic index

LVEF, Left ventricular ejection fraction

LMS, Left main stem

LVSD, Left ventricular systolic dysfunction

MRCA, Magnetic resonance coronary angiography

RCA, Right coronary artery

## Introduction

It is routine practice in patients presenting with a new diagnosis of left ventricular systolic dysfunction (LVSD) to exclude coronary disease as a cause. This is because it is widely believed that patients with coronary disease and LVSD should be offered revascularisation. Some studies such as the STITCH trial have questioned this philosophy, suggesting that patients with established LVSD and coronary artery disease (CAD) do not benefit from revascularisation (1). Other studies have indicated that patients with significant viability benefit (2-4) and that patients with “prognostic” patterns of CAD should be offered revascularisation (5-10). Although no universally agreed definition for prognostically significant coronary disease exists, revascularisation in patients may be recommended in patients with ischaemic LV dysfunction with reversible ischaemia and/or significant viability, even in the absence of angina (11-14).

Invasive coronary angiography has traditionally been used for establishing the presence and pattern of coronary disease. However it is invasive with a small morbidity and mortality and only identifies coronary disease causing luminal obstruction.

Cardiac magnetic resonance (CMR) is an established non-invasive technique for assessing LV function accurately and determining the presence and extent of infarcts in the myocardium. The presence of viability can also be readily determined with good evidence supporting the technique’s ability to predict benefit from revascularisation (15, 16).

Yet, despite the potential advantages, late gadolinium enhancement (LGE) CMR has not gained widespread acceptance as a modality of choice to exclude prognostic CAD. This is predominantly because the evidence for the predictive value of LGE CMR to detect CAD in LVSD is inconsistent with variable sensitivities depending upon the definition of CAD, the patient population, and the use of proximal coronary artery imaging (MRCA). Whilst CMR using a combination of (LGE CMR) with proximal coronary artery imaging by MRCA has been shown to accurately categorise the aetiology of heart failure as ascribed by a consensus panel (17), MRCA is not routinely available in many centres, is time consuming to perform and image quality is unreliable. LGE CMR without

MRCA is a sensitive and specific marker of single vessel CAD in heart failure for those with a previously diagnosed myocardial infarction (18), however, the sensitivity is lower for those without a history of myocardial infarction (80-95%) (19-21). Whilst such false negative rates may be acceptable for non-prognostic single vessel disease, they may not be good enough for the routine exclusion of prognostic CAD. The evidence for the predictive value of LGE CMR alone to detect prognostic CAD in heart failure is lacking and may account for its underutilisation.

This study aimed to assess the ability of late gadolinium CMR alone to exclude prognostically significant CAD in patients with LVSD.

## **Materials and Methods**

### **Patient Population**

We retrospectively identified individuals who had undergone both CMR and X-ray angiography since 2006 until April 2013. The European Society of Cardiology (ESC) imaging criteria for the diagnosis of heart failure with reduced ejection fraction (HFREF) was applied (11, 22). Those with LV ejection fraction (LVEF) <50% or LV end diastolic volume index (LVEDVI)  $\geq 97$  mL/m<sup>2</sup> on CMR, or with a previous echocardiogram suggesting LV systolic impairment for which CMR had been requested to further differentiate the cardiomyopathy were selected. Of these 143 individuals, those with a history of previous revascularisation (n=23), and those who did not receive gadolinium at the time of CMR (n=4) were excluded. A final total of 116 patients were included for data analysis. The sequence of investigations was not defined so that CMR could take place both before or after the X-ray angiogram. The CMR scan was reported by an imaging consultant independently of the X-ray angiogram. The study was considered by the NHS Health Research Authority (HRA) Screening Tool as not requiring individual patient consent.

## **Cardiac Magnetic Resonance**

CMR images were obtained using a 1.5 Tesla GE Signa Excite scanner. Following scout images, ECG-gated, steady-state, free precession breath-hold sequences (typical echo time/repetition time 1.3/3.1 ms, flip angle 45°) were performed to produce three long-axis cines and sequential short axis cines (8mm slices with 2mm gaps) from the atrioventricular ring to the apex of the heart. The LGE images were acquired 10 minutes after intravenous gadolinium-DOTA (Dotarem 0.2 mmol/kg) into a peripheral vein using an inversion recovery gradient-echo sequence. Inversion times were individualised to null normal myocardium (typically 180 to 260ms; pixel size 1.4 x 1.3 mm) and identical views were obtained as for cine imaging except for the removal of basal short axis slices in the LV outflow tract. The scan was reported by a consultant cardiologist with level 3 accreditation in CMR. LVEF and LVEDVI were measured using the standard techniques with the inclusion of papillary muscles in LV volumes (23). LGE was deemed to be present only when signal enhancement could be seen in two planes. It was described as subendocardial, epicardial, transmural or midwall and reported according to the American Heart Association (AHA) 17 segment model in terms of the myocardial segments affected. Subendocardial and transmural LGE was assumed to represent a myocardial infarction due to CAD.

## **X-ray Coronary Angiography**

Invasive X-ray coronary angiography was reported by a consultant cardiologist on the same day as the X-ray angiogram procedure. The presence and degree of any coronary stenoses were labelled on a detailed pictorial display of the coronary arteries along with a written description. Prognostic coronary disease was defined as  $\geq 50\%$  left main stem disease,  $\geq 75\%$  proximal LAD stenosis, or  $\geq 70\%$  stenosis of any 2 or 3 main epicardial coronary arteries. A main epicardial coronary artery was defined as the main LAD or large secondary branch, main Left Circumflex (LCx) or large secondary branch or main right coronary artery (RCA) excluding branches. This definition was based upon combined European and American guidelines, along with other respected trial data that demonstrated

survival benefits in a general or heart failure population when such guideline definitions lacked clarity (5, 8, 12, 14, 24, 25).

## **Data Analysis**

LGE CMR and X-ray angiogram reports were reviewed independently of each other. The definition of prognostic CAD was applied to the X-ray angiogram reports forming two groups: those with prognostic CAD and those without. The presence or absence of subendocardial LGE was determined from the CMR report and two groups were established: those with subendocardial LGE and those without. The presence and quantity of subendocardial LGE was determined for each of the 17 AHA segments (0.5 = <50%, 1 = 50 to 100% segment thickness affected) and then the total amount of subendocardial LGE calculated for each scan to produce a LGE total score. Differences in patient characteristics between those with and without prognostic CAD were assessed using the Student's *t* test, Mann-Whitney U test, or Fisher's exact test depending upon the continuous nature and distribution of the data. Continuous variables were expressed as mean  $\pm$  standard deviation unless otherwise specified. To analyse the accuracy of LGE CMR to detect prognostic CAD we assessed sensitivity, specificity, positive and negative predictive value with 95% confidence intervals, confirmed using exact methods (26, 27). A LGE Score was calculated for each scan with a view to evaluating whether the total amount of LGE could help predict the likelihood of prognostic CAD in positive CMR scans. A value of 1 was given for one AHA segment with transmural enhancement, and 0.5 for one AHA segment with <50% transmural enhancement. A maximum Score of 17 would represent transmural LGE in every AHA segment. The significance of this score was assessed using the Mann-Whitney U test.

## **Results**

A total of 116 patients who had both CMR and X-ray angiography were included for the final analysis. The baseline characteristics are shown in Table 1. Mean age was 64 years and 78% were male. Mean LVEF was 40% and LVEDVI 114 mL/m<sup>2</sup>. The indication for CMR was varied, with the majority (79%) to investigate the aetiology of the LV dysfunction. Other indications included

investigation of left ventricular hypertrophy, ventricular fibrillation/ventricular tachycardia, troponin positive chest pain and valve disease, all in association with LV dysfunction. Patients with a previous history of revascularisation were excluded.

Median time between CMR and angiogram was 42 days: in 41% of cases the CMR was performed before the X-ray angiogram. The diagnostic performance of LGE CMR to predict prognostic CAD is demonstrated in Table 2 and Table 3. The prevalence of prognostic CAD was 47% (95% CI 38 to 57%). The presence of  $\geq 1$  segment of subendocardial LGE detected prognostically significant CAD with a sensitivity of 100% (95% CI, 94 to 100%). The negative predictive value was 100% (95% CI 87 to 100%) and thus false omission rate (the chance of the condition being present amongst those with a negative test) was 0% (95% CI, 0 to 13%). Specificity was 44% (95% CI 32 to 58%) with a false positive rate of 38% (95% CI 28 to 49%).

The sub-analysis of those with false positive LGE CMR investigations demonstrated that 18 patients (53%) had single vessel, non-prognostic CAD that was severe enough to explain the infarct shown on LGE CMR. In the remaining 16 cases (47%), the patients had normal coronaries or only minor CAD with no evidence of a likely culprit for a plaque event. In some of these cases the pattern of LGE was in a single coronary artery territory distribution and in others LGE was present in a multi territory distribution. The differential diagnosis for this group includes true myocardial infarction with recanalization of an occluded artery, coronary spasm, microvascular disease, emboli or infiltrative diseases such as cardiac sarcoid that can be associated with a subendocardial distribution of LGE. Rarely, artefact mimicking LGE would also account for some of these cases.

The mean LGE Score for those with LGE and with prognostic CAD (6.0, SD 2.7) was compared with the mean LGE Score for those with LGE but without prognostic CAD (4.3, SD 3.2) (Table 4). This demonstrated a significant difference between the LGE Scores ( $P=0.007$ ) suggesting that those with smaller LGE scores are less likely to have prognostic CAD. Indeed the 16 cases with LGE but normal or only minor CAD had a mean LGE Score of 1.9 (SD 1.4).

In the 27 patients with true negative results, i.e. non-prognostic coronary disease and no subendocardial LGE, LGE in a midwall or epicardial pattern was seen in 56% of patients. Proposed aetiologies for the cause of LV systolic dysfunction in this group included idiopathic dilated cardiomyopathy, myocarditis, cardiac sarcoid, ARVC with LV involvement and vasculitis. In one of these cases there was single vessel CAD with 100% occlusion of a coronary artery at X-ray angiography but no evidence of an infarct on LGE CMR. Further exploration of this case revealed that the LGE CMR was performed four months before the X-ray angiogram and in the interim period the patient developed exertional chest pain followed by an episode that would be in keeping with a myocardial infarction clinically, and could explain the discrepancy between the imaging studies.

Figure 1 demonstrates the combined X-ray angiography and LGE CMR images for a true positive, false positive and true negative case from this study. Imaging for a false negative case is not provided as this scenario did not occur in this cohort.

## **Discussion**

Our results demonstrate that LGE CMR reliably excludes prognostic CAD in patients with LV systolic dysfunction with 100% sensitivity and negative predictive value. This would support CMR with LGE being used as a first line screening tool in this patient cohort, reserving invasive X-ray coronary angiography for those with subendocardial patterns of LGE.

Specificity was low at 44% (95% CI 32 to 58%) with a false positive rate of 38% (95% CI 28 to 49%) that would necessitate invasive X-ray angiography. However, this high false positive rate can be explained by significant single vessel CAD in over half of the cases which may help justify this rate of pursuing of invasive X-ray angiography. The total LGE Score may aid as an additional helpful indicator of whether prognostic or indeed any significant CAD will be present on X-ray angiography but requires further investigation.

There is no standard definition for prognostically significant CAD amongst the LGE CMR studies. Our definition for prognostic CAD is based on current guidelines and respected trial data (5, 8, 28) and excludes single vessel disease except for left main stem or proximal LAD disease. Previous



groups that have shown moderate ability of LGE CMR to detect CAD used diagnostic thresholds that were less severe than our study and included non-prognostic single vessel disease (19, 20). However, the argument to identify single vessel disease to inform changes to medical management by way of antiplatelet and lipid lowering therapy is contentious in a heart failure population (29, 30). Those with 100% sensitivity have been in cohorts with confirmed myocardial infarctions (18) or have included CMR proximal coronary artery imaging in the protocol (17). This is the first study to assess the utility of LGE CMR without proximal coronary artery imaging to detect prognostically significant CAD.

The evidence supporting revascularisation in LV dysfunction is conflicting but **it may** improve survival in certain settings, providing justification for investigations to identify those who might benefit. Whilst many centres still perform routine X-ray coronary angiography to identify CAD in newly diagnosed LV dysfunction, LGE CMR offers a non-invasive alternative with lower risks and the potential to improve the selection of those patients for whom revascularisation would be of benefit. Limitations of LGE CMR in this setting include circumstances when CAD causes large areas of myocardium to be hibernating but without fibrosis or LGE. Alternatively non-ischaemic causes of LV dysfunction can result in fibrosis and LGE in a subendocardial distribution that might raise false concerns about the presence of significant CAD. Although both of these scenarios have been demonstrated in trials to date (21) and could result in false positive or false negative results, the clinical history in both these circumstances would likely inform alternate conclusions and lead to appropriate recommendations for invasive X-ray coronary angiography.

In our study, there were no false negative results in a cohort with a high prevalence of prognostic CAD supporting the hypothesis we have tested. This is a reassuring demonstration of how CMR scanning using gadolinium late enhancement protocols (without proximal coronary artery imaging) can be used as a screening tool to exclude prognostic CAD and avoid unnecessary invasive X-ray angiography. It is an attribute of CMR which complements the other qualities of this imaging modality in the setting of LV dysfunction, including accurate measurements of left and right

ventricular volumes (31), assessment of pericardial and structural heart disease, and identification of myocardial inflammation or infiltration (18).

## **Limitations**

We acknowledge that the visual grading of vessel stenosis on X-ray angiography is subject to observer interpretation but it is nevertheless the standard method for assessment of the severity of coronary stenoses during routine diagnostic angiography studies.

The study cohort is small and conclusions should be interpreted with this in mind. A large prospective study is now needed to clarify if this high level of sensitivity can be reproduced in a generic newly diagnosed heart failure population using similar definitions for CAD.

## **Conclusions**

The absence of subendocardial LGE on CMR reliably excluded prognostic CAD in patients with LV systolic dysfunction, supporting the use of this modality to avoid unnecessary invasive coronary angiography in this setting.

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**Table 1. Baseline Characteristics**

Characteristic	Entire Group	Prognostic CAD present	Prognostic CAD absent	<i>P</i> value
Number of patients (%)	116 (100%)	55 (47%)	61 (53%)	
Age ( $\pm$ SD)	64 $\pm$ 9	67 $\pm$ 8	61 $\pm$ 10	P=0.001*
Male Sex (%)	90 (78%)	47 (86%)	43 (71%)	P=0.074***
Time between investigations (days $\pm$ IQR)	42 (20 to 83)	41 (21 to 57)	44 (17 to 123)	P=0.619**
CMR LVEF (%) ( $\pm$ SD)	40% $\pm$ 12	41% $\pm$ 11	39% $\pm$ 14	P=0.573**
CMR LVEDVI (mL/m <sup>2</sup> ) ( $\pm$ SD)	114 $\pm$ 31 (n=100)	116 $\pm$ 33 (n=46)	112 $\pm$ 30 (n=54)	P=0.436**

CAD, Coronary artery disease; CMR, Cardiac magnetic resonance; LVEF, Left ventricular ejection fraction; LVEDVI, Left ventricular end diastolic volume indexed to body surface area; IQR, Inter-quartile range; SD, standard deviation. \*Students t test, \*\*Mann-Whitney U test, \*\*\*Fisher's Exact test.

**Table 2. Diagnostic performance of LGE CMR to predict prognostic CAD**

		X-ray angiogram		Total
		Prognostic CAD present	Prognostic CAD absent	
CMR	Subendocardial LGE present	55 (TP)	34 (FP)	89
	Subendocardial LGE absent	0 (FN)	27 (TN)	27
Total		55	61	116

CAD, Coronary artery disease; CMR, Cardiac magnetic resonance; LGE, Late gadolinium enhancement; TP, True positive; FP, False positive; FN, False negative; TN, True negative.

**Table 3. Diagnostic parameters of LGE CMR to predict prognostic CAD**

Performance of LGE CMR (95% Confidence Interval)	
Prevalence of prognostic CAD	47% (38 to 57%)
Sensitivity	100% (94 to 100%)
Specificity	44% (32 to 58%)
Positive Predictive Value	62% (51 to 72%)
Negative Predictive Value	100% (87 to 100%)
False Omission Rate	0% (0 to 13%)

LGE CMR, Cardiac magnetic resonance with late gadolinium enhancement sequences; CAD, Coronary artery disease. Results confirmed by exact methods (26, 27).



**Table 4. Comparison of mean LGE Scores for those with and without prognostic CAD**

	Entire Group	Prognostic CAD present	Prognostic CAD absent	<i>P</i> value
Subendocardial LGE present (%)	89 (77%)	55 (100%)	34 (56%)	
LGE Total Score (mean of all scans $\pm$ SD)	4.1 $\pm$ 3.5	6 $\pm$ 2.7	2.4 $\pm$ 3.2	P<0.001**
LGE Total Score (mean of scans with LGE present $\pm$ SD)	5.3 $\pm$ 3.0	6.0 $\pm$ 2.7 (n=55)	4.3 $\pm$ 3.2 (n=34)	P=0.007**

CAD, Coronary artery disease; LGE, Late gadolinium enhancement; SD, standard deviation. The maximum LGE Total Score = 17 if all segments are transmurally infarcted. \*\*Mann-Whitney U test.

**Figure 1.** X-ray angiography and associated LGE CMR images for true positive, false positive and true negative cases.

Demonstration of three cases: Images A and B demonstrate a true positive case. Images C and D demonstrate a false positive case. Images E and F demonstrate a true negative case. There were no false negative cases in this cohort.

Image A, Coronary angiogram demonstrating prognostic coronary artery disease with > 75% stenosis of the proximal left anterior descending (LAD) artery. Image B, Cardiac magnetic resonance image, demonstrating transmural late gadolinium hyperenhancement in the mid anterior wall and >50% subendocardial hyperenhancement of the basal anterior wall. This is consistent with an infarct in the LAD territory.

Image C, Coronary angiogram, demonstrating normal appearance of the left sided coronary arteries other than distal branch obtuse marginal disease. Image D, Cardiac magnetic resonance image, demonstrating a localised segment of subendocardial hyperenhancement in the posterior wall. The differential diagnosis includes a true myocardial infarction with recanalisation of an occluded artery, coronary spasm, small vessel disease or emboli. Alternatively, Fabry's disease or infiltrative diseases such as cardiac sarcoid should be considered.

Image E, Coronary angiogram, demonstrating normal left sided coronary arteries. Image F, Cardiac magnetic resonance 4-chamber image, demonstrating no evidence of hyperenhancement on late gadolinium imaging.

**Figure 4 – Summary of all images**

